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REMARKS

GENERALLY

Reconsideration of remaining claims 1, 2, 5, 7, 10, and 14-19 of this application is respectfully requested. Claims 3 was previously canceled. Claims 4, 6, 8 and 9 have been canceled by this response without prejudice or disclaimer. Claims 11-13 have been withdrawn by the Examiner as directed to nonelective subject matter. Claims 1, 5, 7, and 10 have been amended. New claims 14-19 have been added. Claims 1, 14, 16, 18 and 19 are in independent format.

35 U.S.C. § 112 REJECTIONS

Prior dependent claim 4 is submitted in independent format as new claim 16. Prior dependent claim 6 is submitted in independent format as new claim 14. Prior dependent claim 8 is submitted in independent format as new claim 18. Prior dependent claim 9 is submitted in independent form at as new claim 19. Original claim 5 is now dependent from claim 16; claim 7 is dependent from claim 14; and claim 10 is dependent from claim 14. Accordingly, it is believed that the claims as now presented traverse the third paragraph of Section 2. of the Examiner's 35 U.S.C. §112 rejection found at the top of page 3 of Examiner's Action. In addition, the second paragraph of Section 2. of the Office Action has been fully traversed by clarifying language in claims 1, 14, and 16 that the hydroxide, chloride, ... recitations apply to each of calcium, magnesium, and potassium respectively.

35 U.S.C. §102/103 AND §103 REJECTIONS

In the Office Action mailed April 20, 2005, the Examiner rejected previously presented claims 1, 2, and 4-13 based on certain prior art patents.

Independent claim 1 remaining in this application has been amended and original claims 5, 7, and 10 have been amended, and new claims 14-19 presented in order to place all of the claims in this application in full condition for allowance, or in better condition for appeal.

The Invention

This invention relates to an improved alkaline dietary and/or therapeutic supplement composition containing an acidic supplement agent having an initial pH less than 6 and an alkaline electrolyte additive with the amount of the additive being sufficient based on the aggregate initial pH of the agent to raise the pH of the combination of the supplement agent and the additive to a level of from about 8 to about 12.5. As a result, the supplement composition upon ingestion with food or a beverage is more effective and the functional utilization of the supplement agent is increased while the alkaline composition is in the person's stomach.

Prior to applicants' invention, there was no recognition in the relevant art that the effectiveness and functional utilization of an initially acidic supplement agent can be enhanced by adding a sufficient amount of an alkaline electrolyte to a normally acidic supplement agent to increase the pH of the composition to from about 8 to about 12.5, and to insure the supplement is carried with the electrolyte. As a result, the supplement composition is alkaline and remains alkaline while in the upper part (cardio) of the person's stomach, where the most efficient absorption of the composition occurs, thereby assuring rapid and enhanced extracellular, intercellular (interstitial), and intracellular movement of the agent into all cell structures of the person's body.

There is no teaching in the art cited by the Examiner of applicants' concept of using the pH of an acidic supplement agent, as the basis for determining the amount of an alkaline electrolyte to be added to the agent to increase the pH of the composition to about 8 to about 12.5, so that the effectiveness and functional utilization of the supplement in the person's body is enhanced because of absorption of the supplement agent in the person's stomach rather than beyond the stomach in the individual's intestines.

The Rejections Are Based on Conjecture, Speculation and Unsupported Assumptions

Recognizing that the cited references are deficient in major respects, the Examiner resorts to conjecture, speculation, and unsupported assumptions as to what the references in fact teach. Exemplary are the assertions that the claimed functional attributes of the present claimed invention "*would be inherent* in the reference composition[s]," "it would *appear* that the reference composition[s] *must* also function in the manner instantly claimed" and that the compositions of the references "would also *appear* to exhibit the claimed functional characteristics." The Examiner therefore concludes, notwithstanding the acknowledged deficiencies of each of the references relied upon, the claimed invention is anticipated or is obvious from the cited patents.

"Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re: Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

"In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics *necessarily* flows from the teachings of the applied prior art." *Ex Parte Levey*, 17 USPQ2d 1461, 1464 (Bd. App. & Inter. 1990).

Herschler `547 Patent

It is asserted that the `547 Herschler patent teaches the combination of methylsulfonylmethane (MSM) with ascorbic acid and bioflavonoids. The Examiner acknowledges that the reference does not teach:

(1) that the therapeutic agents have a pH of 6 or less;

(2) that the therapeutic agents have limited availability because the pH of each is 6 or less; and

(3) that the provision of sufficient alkaline electrolyte additive to raise the pH of the composition to about 8 to about 12.5 improves the effectiveness of the composition in the stomach.

First, Herschler states that a minor amount of calcium carbonate may optionally be added as a tableting agent, "e.g., up to about 5% by weight." (Col. 4, ll. 63-65) Although there is no direct or implied disclosure in Herschler of incorporating a sufficient amount of an alkaline electrolyte additive in his pharmaceutical agent that includes MSM includes to increase the pH of the agent to a level of from about 8 to about 12.5, applicant's composition contains more that 5% of the alkaline electrolyte. The remaining claims have been amended to recite that the alkaline agent is present at a level of at least about 8% by weight of the composition, well above the 5% ceiling of Herschler. Support for the at least about 8% recitation is found in the Example at page 14 (1800 mg. of the agent and 150 mg. of the alkaline electrolyte, i.e., 8.3% electrolyte) and the Example at pages 15 and 16 (1800 mg. of the agent and 200 mg. of the alkaline electrolyte, i.e., 11.1% electrolyte).

Herschler incorporates a small amount of calcium carbonate in his MSM formulation only as a filler or a tableting agent, not to enhance the effectiveness and functionality of the MSM in the person's body, and especially absorption of the agent in the individual's stomach. Herschler does not suggest incorporating an amount of an alkaline electrolyte additive to the formulation that is sufficient based on the aggregate initial pH of the agent to raise the pH of the combination of the supplement agent and the additive to a pH from about 8 to about 12.5 to cause rapid extracellular, intercellular, and intracellular movement of the agent into all cell structures of the person's body.

Stroppolo `312 Patent

The Stroppolo patent is concerned with combining arginine with naporoxen, which is said to hasten the analgesic effect of the drug and its lasting effect. Sodium or potassium bicarbonate is optionally added to the formulation as an effervescent agent so that if the product is dissolved in water, the resultant aqueous solution has a pH from 7.5 to 9. Furthermore, the sodium or potassium bicarbonate is said to improve the rheological characteristics of the mixture making it particularly suitable for granulation and then compression into a tablet.

The supplement composition as set forth in the remaining claims of this application consists essentially of an agent selected from the group consisting of water soluble vitamins, bioflavonoids, minerals, trace minerals, phytonutrients, and herbs, all of which have initial pH of 6 or less. Arginine, an essential amino acid, is not in the class of agents called for by the present claims, but is an essential component of Stroppolo's formulation. The "consisting essentially of" format of the claims of this application rules out the inclusion of an amino acid such as arginine.

As is the case with the rejection based on the `547 Herschler patent, the Examiner acknowledges that Stroppolo does not teach that the effectiveness and functional utilization of therapeutic agents having a pH of 6 or less and therefore of limited availability can be significantly enhanced by using the aggregate pH of the therapeutic agent as a basis for determining how much alkaline electrolyte should be added to the therapeutic agent to bring the pH of the combination to a pH of 8 to 12.5. By doing so, absorption of the composition occurs rapidly and efficiently in the person's stomach rather than in the individual's intestines to cause rapid extracellular, intracellular and intercellular movement of the agent into all cell structures of the person's body.

Herschler `039 Patent

The `039 Herschler patent relates only to combining a commercial dental product with methylsulfonylmethane on a 50/50 w/w basis. There is not mention in this patent of addition of an alkaline electrolyte for increasing the pH of the methylsulfonylmethane.

Lysaght `093 Patent

The Lysaght patent relates to a method of treating arthritis by administration of a composition containing calcium carbonate and magnesium sulfate. A preferred formulation is made of cobalt chloride, potassium iodide, calcium carbonate and magnesium sulfate. The patentee states that addition of a cobalt compound alleviates the adverse effects of arthritis. Calcium carbonate is included in the patentee's formulation, not as an electrolyte for raising the pH of the composition to a designated alkaline level, but instead "serves as a *bone strengthener*." (Col. 1, ll. 51-52)

A substitute for cobalt chloride is said to be cyanocobalamin (vitamin B_{12}), which has a neutral pH of about 7.16 and therefore is not one of the supplement agents called for in the claims of this application. Lysaght tailors his formulation so that it passes through the stomach into the small intestine to the ilium (end of the small intestine) where the formulation is finally absorbed, whereas in the present invention, the supplement agent and the electrolyte are absorbed in the individual's upper (cardio) stomach.

As explained in the attachments, Exhibits A- G, vitamin B_{12} is absorbed in the ilium and not in the stomach. Cobalt chloride would be similarly absorbed outside of the stomach.

Schinitsky '551 Patent

The Schinitsky patent is directed solely to treatment of arthritis with glucosamine and does not disclose addition of an alkaline electrolyte to raise the pH of the composition to a level of 8 to 12.5.

CLAIMS PATENTABLY DISTINGUISH OVER THE CITED ART

The claims remaining in this application fully distinguish over each of the references, both on the basis of the provisions of Section 102 when combined with Section 103, and/or under Section 103. Therefore, applicants respectfully request that a timely Notice of Allowance of claims 1, 2, 5, 7, 10, and 14-19 be issued in this case. Should the Examiner have any questions, please contact the undersigned at (800) 445-3460.

A one-month Petition for Extension of Time accompanies this Amendment, along with a check in the amount of $60.00 for the petition fee set forth in 37 C.F.R. § 1.17(a). The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 19-0522.

Respectfully submitted,

HOVEY WILLIAMS LLP

Date: August 22, 2005

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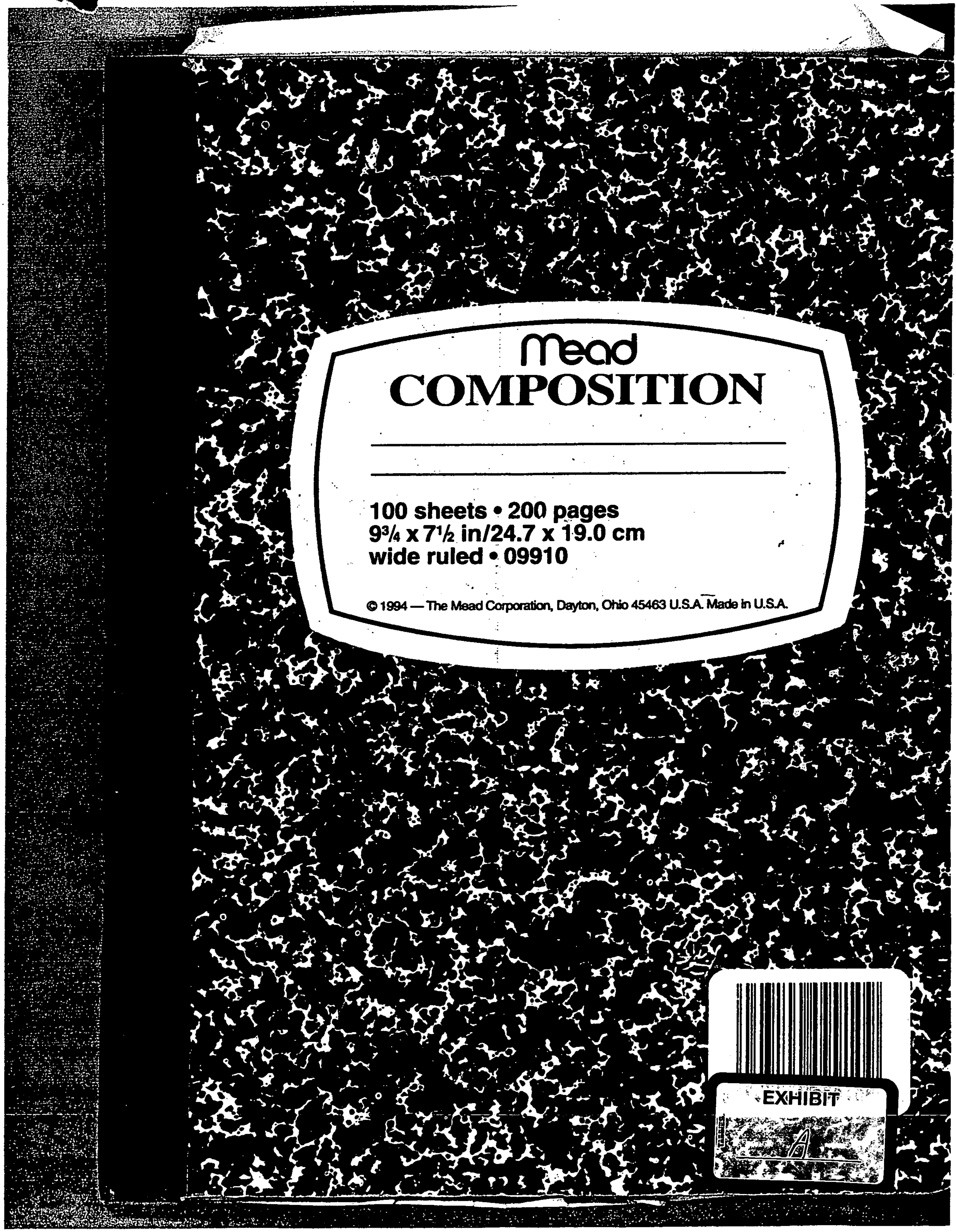
[Attachments: Exhibits A-F]



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COMPOSITION

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EXHIBIT
A

3/13/97	DIH2O	supplement
B1	7.01	6.74
B2	6.96	7.58
B5	6.96	7.13
B6	6.92	2.69
B12	6.95	7.16

23.9C
Buffer 7.02

Diagram of digestion

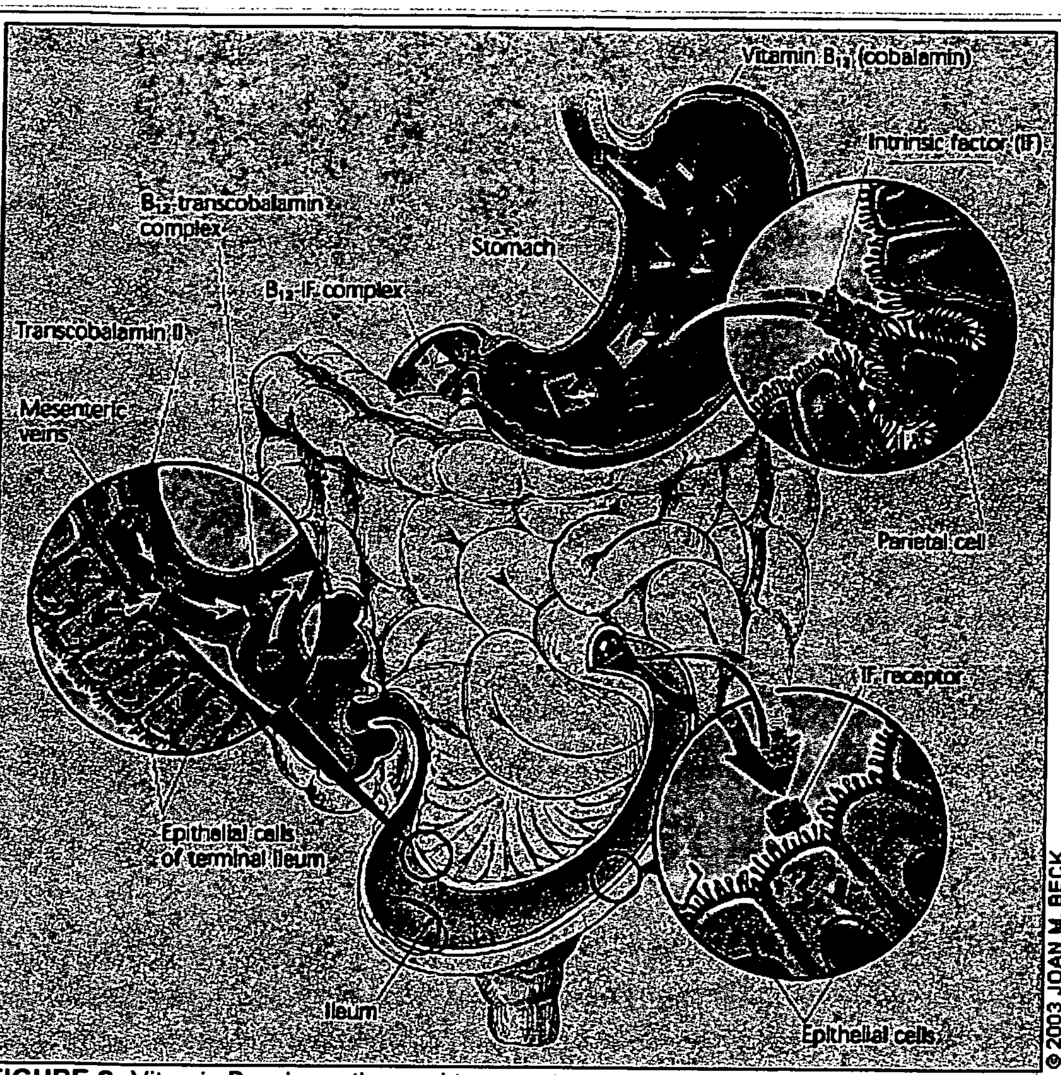

FIGURE 2. Vitamin B_{12} absorption and transport.

EXHIBIT
B

B 12 why sublingual

http://www.sublingualb12.com/sublingual_science.htm

Here is why you might not be getting your B-12 with those other vitamins!

When the B-12 vitamin enters your body in the stomach (through food or oral pills), acids in the stomach separate the B-12 from its protein source. It then must combine with intrinsic factor cells in the stomach. This B-12/intrinsic factor complex travels to your intestine, where it is absorbed in the terminal ileum. The absorbed complex is then transported via blood plasma and stored in the liver.

The interruption of any of these steps affects your body's ability to absorb B-12. Here is a list of common interruptions to B-12 absorption:

1. As you age (over 45) or become overly reliant on acid suppressing agents like antacids, your ability to produce gastric acids in the stomach decreases, meaning that the B-12 is less likely to be released from its food source.
2. An autoimmune or other disease reduces the production or blocks the action of intrinsic factor, resulting in intestinal malabsorption.
3. People with pernicious anemia have decreased production of intrinsic factor.
4. **Abdominal surgery** reduces B-12 absorption.
    - Gastrectomy eliminates the site of intrinsic factor production.
    - Blind loop syndrome results in competition for vitamin B-12 by bacterial overgrowth in the lumen of the small intestine.
    - Surgical resection of the ileum eliminates the site of vitamin B-12 absorption.
5. Pancreatic insufficiency such as fish tapeworm infection and severe Crohn's disease affect absorption.

http://www.postgradmed.com/issues/2001/07_01/dharmarajan.htm

This document is a partial document …

Approaches to vitamin B_{12} deficiency

Early treatment may prevent devastating complications

T. S. Dharmarajan, MD; Edward P. Norkus, PhD

VOL 110 / NO 1 / JULY 2001 / POSTGRADUATE MEDICINE

CME learning objectives

- To understand the complex process of absorption of vitamin B_{12} and how a defect in any step can lead to deficiency
- To learn that patients with vitamin B_{12} deficiency may be asymptomatic or may present with a wide spectrum of hematologic or neuropsychiatric manifestations
- To become familiar with correction of vitamin B_{12} deficiency and how to maintain adequate body stores for life

The authors disclose no financial interest in this article.

Preview: Vitamin B_{12} deficiency is a common problem that affects the general population and the elderly in particular. Persons with the deficiency may be asymptomatic or may have hematologic or neuropsychiatric signs and symptoms. If the disorder is untreated, complications may cause significant morbidity. In this article, Drs Dharmarajan and Norkus discuss approaches to screening and diagnosis as well as the nontoxic, low-cost treatments now available.

Dharmarajan TS. Approaches to Vitamin B_{12} deficiency: early treatment may prevent devastating complications. Postgrad Med 2001;110(1):99-105

EXHIBIT

TABBIES

C

Vitamin B_{12}, also known as cobalamin, was first isolated in 1948 and immediately shown to be effective in the treatment of pernicious anemia (1). Recently, interest in the vitamin has been renewed because of the recognition that cobalamin deficiency occurs in 3% to 40% of the general population (2-7). Our own studies of community, hospital, and nursing home subjects (3,7) found the prevalence to be 15% to 25%. The most recent Food Guide Pyramid for persons over age 70 features a flag to emphasize the importance of adequate daily B_{12} intake (8).

Sources and chemistry

As a required nutrient, vitamin B_{12} is obtained primarily from animal proteins (ie, red meat, poultry, fish, eggs, and dairy); plants and vegetables lack the vitamin unless they have been contaminated by soil microorganisms (9). Thus, ovolactovegetarians and lactovegetarians obtain adequate cobalamin, but vegans risk deficiency (9). There are two commercial forms of B_{12}: cyanocobalamin crystalline, which is available in the United States, and hydroxocobalamin crystalline, available in Europe. Enzymatic removal of the cyano group from cyanocobalamin is required to create the active molecule (1,10).

Absorption, storage, and elimination

Absorption of vitamin B_{12} from foods is complex; a defect in any step can lead to deficiency. In the stomach, gastric acid and pepsin release cobalamin from animal proteins, and it binds preferentially to salivary R protein. In the upper small intestine, pancreatic enzymes and an alkaline pH digest the R protein-cobalamin complex. B_{12} then binds to intrinsic factor (IF) to form an IF-cobalamin complex. Endogenous B_{12}, excreted in bile, also binds to IF. The IF-cobalamin complex attaches to membrane receptors in the ileum and is absorbed through endocytosis. Absorption of vitamin B_{12} by this process is limited (<3 micrograms per meal). About 1% of the B_{12} dose is absorbed by passive diffusion even in the absence of IF (1,11).

The liver contains most of the body's cobalamin (about 1.5 mg), followed by the kidneys, heart, spleen, and brain. Normal body stores of vitamin B_{12} range from 2 to 10 mg; daily losses are 2 to 5 micrograms. Over 75% of the cobalamin excreted in bile is reabsorbed. Urinary excretion of cobalamin usually is low (10). Because of this efficient enterohepatic circulation, vitamin B_{12} deficiency typically takes many years to develop. The latest Recommended Dietary Allowance (RDA) for vitamin B_{12} is 2.4 micrograms/day for persons aged 14 to 70 years; the average diet in the United States contains about 5 micrograms daily (6).

Function

Two cobalamin-dependent enzymatic reactions occur in humans. The first reaction converts methylmalonyl-coenzyme A (CoA) to succinyl-CoA using cobalamin as a cofactor. Vitamin B_{12} deficiency leads to an increase in serum methylmalonyl-CoA and its metabolic product, methylmalonic acid (MMA). The second reaction uses cobalamin as a cofactor in the synthesis of methionine from homocysteine. Deficiency in B_{12} leads to an accumulation of homocysteine. Thus, both MMA and homocysteine levels increase in vitamin B_{12} deficiency. Homocysteine levels also increase in folic acid deficiency (12), vitamin B_6 deficiency, renal failure, and hypothyroidism as well as in aging persons and persons with a genetic defect involving cystathionine beta-synthase (13,14). Thus, an elevated MMA level is viewed as a more specific marker for vitamin B_{12} deficiency except in chronic renal failure, in which MMA increases independently of B_{12} levels.

Conditions that affect absorption

Table 1 summarizes several conditions and mechanisms that affect absorption of vitamin B_{12} from the intestine (4,12). Pernicious anemia, once believed to be the most common cause of vitamin B_{12} deficiency (15), may account for only a small percentage of cases (4). Deficiency most often results from food-cobalamin malabsorption due to gastric dysfunction that may be exacerbated by the use of acid-lowering agents (eg, proton pump inhibitors, histamine$_2$ receptor antagonists) (16,17). Certain other drugs (eg, cholestyramine [LoCHOLEST, Prevalite, Questran], *p*-aminosalicylate, metformin hydrochloride [Glucophage], colchicine) cause malabsorption through effects on the ileal mucosa or membrane receptors or by other means (10).

injections. This route is contraindicated in patients who have nasal diseases or are receiving other medications simultaneously in the same nostril. Intranasal B_{12} offers the advantage of delivery by the patient or caregiver (25).

In the absence of IF, oral administration of a dose consistent with the RDA level is unlikely to prove beneficial, particularly in patients with pernicious anemia and those who have undergone gastrectomy. Even in the absence of IF, about 1% of the oral dose is absorbed from the intestine by simple diffusion (1,11). Thus, in pernicious anemia, vitamin B_{12} must be given in large amounts (preferably >1,000 micrograms a day) (5,26). However, in vegan patients or those with malabsorption of cobalamin from food and low gastric acidity, oral B_{12} may be effective in smaller doses (9). The bioavailability of B_{12} from multivitamin preparations is difficult to predict (27). Finally, patient compliance remains a significant concern with oral B_{12} treatment, particularly in elderly patients and those with dementia (26).

We believe that vitamin B_{12} deficiency should be initially corrected with intramuscular administration followed by intramuscular, intranasal, or oral therapy. When cobalamin is reliably administered by either parenteral or intranasal routes, follow-up measurement of serum B_{12} levels should be unnecessary. Therapy should be continued even if B_{12} levels improve, because they will likely decrease over time and the risk of deficiency recur (14).

Summary

Vitamin B_{12} deficiency affects about one quarter of the US population and is more common in the elderly and in adults with several predisposing conditions. Diagnosis is easy with the many available laboratory tests. Healthcare professionals need to recognize that vitamin B_{12} deficiency is often undetected and can lead to devastating and irreversible complications. Early treatment is effective and prevents disability from hematologic or neuropsychiatric complications, or both. Today, physicians have a choice of several inexpensive treatments that are easy to administer and have no known side effects.

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B 12 absorption

http://ods.od.nih.gov/factsheets/vitaminb12.asp
Dietary Supplement Fact Sheet: Vitamin B12
Office of Dietary Supplements • Warren G. Magnuson Clinical Center • National Institutes of Health

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What is vitamin B_{12}?

Vitamin B_{12} is also called cobalamin because it contains the metal cobalt. This vitamin helps maintain healthy nerve cells and red blood cells [1-4]. It is also needed to help make DNA, the genetic material in all cells [1-4].

Vitamin B_{12} is bound to the protein in food. Hydrochloric acid in the stomach releases B_{12} from proteins in foods during digestion. Once released, vitamin B_{12} combines with a substance called gastric intrinsic factor (IF). This complex can then be absorbed by the intestinal tract.

What foods provide vitamin B_{12}?

Vitamin B_{12} is naturally found in animal foods including fish, meat, poultry, eggs, milk, and milk products. Fortified breakfast cereals are a particularly valuable source of vitamin B_{12} for vegetarians [5-7]. Table 1 lists a variety of food sources of vitamin B_{12}.

Table 1: Selected food sources of vitamin B_{12} [5]

Food	Micrograms (µg) per serving	Percent DV*
Mollusks, clam, mixed species, cooked, 3 ounces	84.1	1400
Liver, beef, braised, 1 slice	47.9	780
Fortified breakfast cereals, (100%) fortified), ¾ cup	6.0	100
Trout, rainbow, wild, cooked, 3 ounces	5.4	90
Salmon, sockeye, cooked, 3 ounces	4.9	80
Trout, rainbow, farmed, cooked, 3 ounces	4.2	50
Beef, top sirloin, lean, choice, broiled, 3 ounces	2.4	40
Fast Food, Cheeseburger, regular, double patty & bun, 1 sandwich	1.9	30
Fast Food, Taco, 1 large	1.6	25
Fortified breakfast cereals (25% fortified), ¾ cup	1.5	25
Yogurt, plain, skim, with 13 grams protein per cup, 1 cup	1.4	25
Haddock, cooked, 3 ounces	1.2	20
Clams, breaded & fried, ¾ cup	1.1	20
Tuna, white, canned in water, drained solids, 3 ounces	1.0	15
Milk, 1 cup	0.9	15
Pork, cured, ham, lean only, canned, roasted, 3 ounces	0.6	10
Egg, whole, hard boiled, 1	0.6	10
American pasteurized cheese food, 1 ounces	0.3	6
Chicken, breast, meat only, roasted, ½ breast	0.3	6

*DV = Daily Value. DVs are reference numbers developed by the Food and Drug Administration (FDA) to help consumers determine if a food contains a lot or a little of a specific nutrient. The DV for vitamin B_{12} is 6.0 micrograms (µg). Most food labels do not list a food's vitamin B_{12} content. The percent DV (%DV) listed on the table indicates the percentage of the DV provided in one serving. A food providing 5% of the DV or less is a low source while a food that provides 10-19% of the DV is a good source. A food that provides 20% or more of the DV is high in that nutrient. It is important to remember that foods that provide lower percentages of the DV also contribute to a healthful diet. For foods not listed in this table, please refer to the U.S. Department of Agriculture's Nutrient Database Web site:

http://www.nal.usda.gov/fnic/cgi-bin/nut_search.pl.

What is the recommended dietary intake for vitamin B_{12}?

Recommendations for vitamin B_{12} are provided in the Dietary Reference Intakes (DRIs) developed by the Institute of Medicine of the National Academy of Sciences [7]. *Dietary Reference Intakes* is the general term for a set of reference values used for planning and assessing nutrient intake for healthy people. Three important types of reference values included in the DRIs are *Recommended Dietary Allowances* (RDA), *Adequate Intakes* (AI), and *Tolerable Upper Intake Levels* (UL). The RDA recommends the average daily intake that is sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in each age and gender group [7]. An AI is set when there is insufficient scientific data available to establish a RDA. AIs meet or exceed the amount needed to maintain a nutritional state of adequacy in nearly all members of a specific age and gender group [7]. The UL, on the other hand, is the *maximum* daily intake unlikely to result in adverse health effects [7]. Table 2 lists the RDAs for vitamin B_{12}, in micrograms (µg), for children and adults.

Table 2: Recommended Dietary Allowances (RDA) for vitamin B_{12} for children and adults [7]

Age (years)	Males and Females (µg/day)	Pregnancy (µg/day)	Lactation (µg/day)
1-3	0.9	N/A	N/A
4-8	1.2	N/A	N/A
9-13	1.8	N/A	N/A
14-18	2.4	2.6	2.8
19 and older	2.4	2.6	2.8

There is insufficient information on vitamin B_{12} to establish a RDA for infants. Therefore, an Adequate Intake (AI) has been established that is based on the amount of vitamin B_{12} consumed by healthy infants who are fed breast milk [7]. Table 3 lists the Adequate Intakes for vitamin B_{12}, in micrograms (µg), for infants.

Table 3: Adequate Intake for vitamin B_{12} for infants [7]

Age (months)	Males and Females (µg/day)
0-6 months	0.4
7-12 months	0.5

When is a deficiency of vitamin B_{12} likely to occur?

Results of two national surveys, the National Health and Nutrition Examination Survey (NHANES III-1988-94) [8] and the Continuing Survey of Food Intakes by Individuals (CSFII 1994-96) found that most children and adults in the United States (U.S.) consume recommended amounts of vitamin B_{12} [6-8]. A deficiency may still occur as a result of an inability to absorb B_{12} from food and in strict vegetarians who do not consume any animal foods [9]. As a general rule, most individuals who develop a vitamin B_{12} deficiency have an underlying stomach or intestinal disorder that limits the absorption of vitamin B_{12} [10]. Sometimes the only symptom of these intestinal disorders is subtly reduced cognitive function resulting from early B_{12} deficiency. Anemia and dementia follow later [1,11].

Signs, symptoms, and health problems associated with vitamin B_{12} deficiency

- Characteristic *signs, symptoms, and health problems associated with B_{12} deficiency* include anemia, fatigue, weakness, constipation, loss of appetite, and weight loss [1,3,12].
- Deficiency also can lead to neurological changes such as numbness and tingling in the hands and feet [7,13].
- Additional symptoms of B_{12} deficiency are difficulty in maintaining balance, depression, confusion, dementia, poor memory, and soreness of the mouth or tongue [14].
- Signs of vitamin B_{12} deficiency in infancy include failure to thrive, movement disorders, delayed development, and megaloblastic anemia [15].

Many of these symptoms are very general and can result from a variety of medical conditions other than vitamin B_{12} deficiency. It is important to have a physician evaluate these symptoms so that appropriate medical care can be given.

Do pregnant and/or lactating women need extra Vitamin B_{12}?

During pregnancy, nutrients travel from mother to fetus through the placenta. Vitamin B_{12}, like other nutrients, is transferred across the placenta during pregnancy. Breast-fed infants receive their nutrition, including vitamin B_{12}, through breast milk. Vitamin B_{12} deficiency in infants is rare but can occur as a result of maternal insufficiency [15]. For example, breast-fed infants of women who follow strict vegetarian diets have very limited reserves of vitamin B_{12} and can develop a vitamin B_{12} deficiency within months of birth [7,16]. This is of particular concern because undetected and untreated vitamin B_{12} deficiency in infants can result in permanent neurologic damage. Consequences of such neurologic damage are severe and can be irreversible. ***Mothers who follow a strict vegetarian diet should consult with a pediatrician regarding appropriate vitamin B_{12} supplementation for their infants and children*** [7]. They should also discuss their own need for vitamin B_{12} supplementation with their personal physician.

Who else may need a vitamin B_{12} supplement to prevent a deficiency?

- Individuals with pernicious anemia or with gastrointestinal disorders may benefit from or require a vitamin B_{12} supplement.
- Older adults and vegetarians may benefit from a vitamin B_{12} supplement or an increased intake of foods fortified with vitamin B_{12}.
- Some medications may decrease absorption of vitamin B_{12}. Chronic use of those medications may result in a need for supplemental B_{12}.

Individuals with pernicious anemia

Anemia is a condition that occurs when there is insufficient hemoglobin in red blood cells to carry oxygen to cells and tissues. Common signs and symptoms of anemia include fatigue and weakness. Anemia can result from a variety of medical problems, including deficiencies of vitamin B_{12}, vitamin B_6, folate and iron. Pernicious anemia is the name given more than a century ago to describe the then-

Handbook of Vitamins, Minerals and Hormones

SECOND EDITION

EXHIBIT

D

About Calcium

8. Metalloenzymes Cofactors, Metalloproteins 8, 10, 11, 15, 18, 25, 30, 32, 35, 50, 51, 53

System Type	*Organ*	*Metallo-enzyme/Protein*	*Cofactors*	*System Function*
Metallo-protein Cofactor	Muscle	Troponin	Ca^{2+}	Contraction of muscle
	Endocrine glands	Adenyl cyclase	Ca^{2+}	Inhibition of C-AMP
	Bone, Kidney	Kinases	Ca^{2+}	Stimulated (form PO_4-proteins)
	Nerves	Choline esterase	Ca^{2+}	Destruction of acetycholine
	Blood	Prothrombin	Ca^{2+}	Formation of thrombin, blood clotting
	Pancreas	Lipase	Ca^{2+}	Fat digestion
	Liver	Succinic deHase	Ca^{2+}	Krebs cycle
	Muscle	ATP-ase	Ca^{2+}	ATP → ADP (muscle energy)

9. Excretion 18, 20, 21, 30, 39, 51

Chemical forms—Urine (phosphate, citrate, Ca^{2+} ion, chlorides), feces (bile compounds, phytates, oxalates, PO_4, Ca soaps)

Organs—Kidney (urine): 15-20%; intestine (feces): 70-80%; liver (bile, intestine): some reabsorption; skin: 2-5%; other: 0

MISCELLANEOUS

1. Relationship to Other Minerals 18, 27, 30, 51, 53

Mg—Absorption antagonist, synergist in bone and metabolism
Na—Antagonist or synergist to Ca, depending on organ and concentration
K—Antagonist or synergist to Ca, depending on organ and concentration
PO_4—Absorption synergist (antagonist in excess Ca), synergist in bone
F—Absorption antagonist
Fe—Utilization stimulated by Ca (hematopoiesis)

2. Relationship to Vitamins 18, 27, 36, 37, 51, 53

Vitamin D—Synergist in absorption
Vitamin A—Synergist in absorption
Vitamin C—Synergist in bone growth

No relation to B12 absorption

2. **Relationship to Vitamins** 18, 27, 36, 37, 51, 53
   B_6—Involved in electrolyte balance
   D—Involved in Ca-K antagonisms in absorption (?)

3. **Relationship to Hormones** 18, 20, 27, 50, 51, 53
   FSH—K increases secretion of FSH
   ADH—K increases ADH output
   Aldosterone—K increases aldosterone output
   Insulin—K is synergistic to insulin
   STH—is synergistic to K in growth

4. **Unusual Features** 18, 21, 27, 30, 36, 50, 51, 53
   K is major ion involved in heart action
   Absorption mechanisms for K remain a mystery
   K causes liquefaction of intracellular fluid
   Pure K salt solutions are toxic to cells, cause nerves to lose irritability
   K causes increase in cell permeability
   Ionophore transport of K

5. **Possible Relationship of Deficiency Symptoms to Metabolic Action** 18, 21, 27, 30, 35, 51, 53
   Muscle weakness—Loss of nerve irritability
   Cardiac arrhythmia—Heart regulation lost
   Paralysis—High Na/K paralyzes nerves
   Bone fragility—Loss of Ca synergism
   Sterility—Loss of FSH action
   Adrenal hypertrophy—Stress reactions
   Decreased bone growth—Loss of growth
   Loss of weight—Loss of synergism with protein, CHO metabolism

About B12

Medium: 5-50 μg/100 g
  Kidney (rabbit)
  Liver (rabbit, chicken)
  Heart (beef, rabbit, chicken)
  Egg yolk
  Clams, sardines, salmon, crabs, oysters, herring
Low: 0.5-5 μg/100 g
  Cod, flounder, haddock, halibut, lobster, scallop, shrimp, swordfish, tuna, whale
  Beef, pork lamb, chicken
  Cheeses, milk, eggs

MEDICAL AND NUTRITIONAL ROLE

1. **Units** 8, 16, 17, 26, 34
   1 USP = 1 μg vitamin B_{12} = 11,000 LLD units (*L. lactis Dorner* units)

2. **Normal Blood Levels (Man)** 4, 14, 26, 33, 34
   .02-.09 μg/100 ml, serum; .016-.020 μg/100 ml, RBC

3. **Recommended Allowances** 4, 8, 21, 24, 27, 37
   Children—2.0-3.0 μg/day
   Adults—3.0 μg/day
   Special—Pregnancy, 4 μg/day; lactation, 4 μg/day; intestinal malabsorption or disease; anorexia; old age; neuropathies; malnutrition; alcoholism
   Therapeutic dose—1-2 μg/day (I.M.)

4. **Administration** 8, 9, 31, 32, 35
   Injection—Parenteral, intramuscular (I.M.)
   Topical—No data
   Oral—Not very effective unless intrinsic factor (enzyme) present

5. **Factors Affecting Availability** 3, 8, 20, 27, 27a
   Decrease
     Cooking losses—Heat-labile
     Cobalt deficiency (ruminants)
     Intestinal malabsorption or parasites
     Lack of Intrinsic Factor
     Intestinal disease, aging
     Vegetarian diet
     Excretion in feces
     Gastrectomy

Increas
  Adm
  Synt
  Redu
  Foo
  Ca^{2+}

6. **Deficie**
   Poor gr
   Increas
   Megalo
   Macroc
   Glossiti
   Degene
   Decreas
   Disturb
   Leukop
   Gastroi
   Loss of
   Poor fe
   Reprod
   Porphyr
   Dermati
   Impaire

7. **Effects**
   Polycyt
   General

1. **Biosynt**
   Precurs
     Glyci
     δ-Am
     Meth
   Interme
     Porp
     α-*d*-R
     5,6-D
     α-Rib

2. **Production** 3, 19, 25, 28
   Species—Bacteria (some); actinomycetes (some)

3. **Storage** 8, 9, 16, 26, 34
   Liver (30-60%), lungs, kidneys, spleen

4. **Blood Carriers** 8, 14, 29, 31, 32
   α_1-Globulins (52%), α_2-globulins (21%), albumins (16%), β-globulins (7
   γ-globulins (6%)

5. **Half-life** 8, 9, 29, 31, 32, 34
   >1 year

6. **Target Tissues** 14, 16, 29, 31, 32, 34
   Central nervous system, kidneys, myocardium, muscle, skin, bone

7. **Reactions** 5, 14, 16, 17, 28
   Coenzyme forms
   - Adenyl cobamide coenzyme (adenyl nucleoside)
   - 5,6-Dimethylbenzimidazolylcobamide coenzyme
   - Benzimidazolylcobamide coenzyme

Organ	*Enzyme System*	*Effect*
	MUTASES	
Liver	Glutamate mutase (glutamic-aspartic)	Activate
Liver	Methylmalonyl CoA mutase (methyl malonic-succinic)	Activate
	DEHYDRASES	
Liver	Diol dehydrase (glycerol-1,3-propanediol)	Activate
Liver	Glycerol dehydrase (glycerol-β-OH-propionaldehyde)	Activate
Liver	Ethanolamine deaminase (ethanolamine-ammonia, acetaldehyde)	Activate
	TRANSMETHYLASES	
Liver	B_{12} enzyme (homocysteine-methionine) with folate	Activate
Liver	Thymidine synthesis enzymes (purine biosynthesis)	Activate
	REDUCTASES	
Liver	Methane formation enzymes	Activated
Liver	Ribonucleotide reductase (ribonucleotide-deoxyribonucleotide)	Activated
Liver	Lysine fermentation enzymes	Activated
Liver	Acetate synthesis enzymes	Activated

See pg 3 of this

B12 and potassium

http://www.caromont.org/16054.cfm

Vitamin B12, an essential nutrient, is also known as cobalamin. The "cobal" in the name refers to the metal cobalt contained in B12. Vitamin B12 is required for the normal activity of nerve cells, and works with folate and vitamin B6 to lower blood levels of homocysteine, a chemical in the blood that might contribute to heart disease. B12 also plays a role in the body's manufacture of S-adenosylmethionine, or SAMe.

Anemia is usually (but not always) the first sign of B12 deficiency. Earlier in this century, doctors coined the name "pernicious anemia" for a stubborn anemia that didn't improve even when the patient was given iron supplements. Today we know that pernicious anemia is usually caused by a condition in which the stomach fails to excrete a special substance called intrinsic factor. The body needs the intrinsic factor for efficient absorption of vitamin B12. In 1948, vitamin B12 was identified as the cure for pernicious anemia. B12 deficiency also causes nerve damage, and this may in some cases occur without anemia first developing.

Vitamin B12 has also been proposed as a treatment for numerous other conditions, but as yet there is no definitive evidence that it is effective for any purpose other than correcting deficiency.

Requirements/Sources

Extraordinarily small amounts of vitamin B12 suffice for daily nutritional needs. The official U.S. and Canadian recommendations for daily intake are as follows:

Infants 0-6 months, 0.4 mcg
7-12 months, 0.5 mcg
Children 1-3 years, 0.9 mcg
4-8 years, 1.2 mcg
9-13 years, 1.8 mcg
Males and females 14 years and older, 2.4 mcg
Pregnant women, 2.6 mcg
Nursing women, 2.8 mcg

EXHIBIT E

Vitamin B12 deficiency is rare in the young, but it's not unusual in older people: Probably 10 to 20% of the elderly are deficient in B12.1-4 This may be because older people have lower levels of stomach acid. The vitamin B12 in our food comes attached to proteins, and must be released by acid in the stomach in order to be absorbed. When stomach acid levels are low, we don't absorb as much vitamin B12 from our food. Fortunately, vitamin B12 supplements don't need acid for absorption. For this reason, people who take medications that greatly reduce stomach acid, such as Prilosec (omeprazole) or Zantac (ranitidine), should probably also take B12 supplements.5-10

Stomach surgery and other conditions affecting the digestive tract can also lead to B12 deficiency. Vitamin B12 absorption or levels in the blood may also be impaired by colchicine (for gout), metformin and phenformin (for diabetes), and AZT (for AIDS).11,12 Exposure to nitrous oxide (such as may be experienced by dentists and dental hygienists) might cause B12 deficiency, but studies disagree.14,15 Slow-release potassium supplements might impair B12 absorption as well.17

Vitamin B12 is found in most animal foods; it is also found only in animal food. Beef, liver, clams, and lamb provide a whopping 80 to 100 mcg of B12 per 3.5-ounce serving, at least 40 times the dietary requirement. Sardines, chicken liver, beef kidney, and calf liver are also good sources, providing between 25 and 60 mcg per serving. Trout, salmon, tuna, eggs, whey, and many cheeses provide at least the recommended daily intake. Note: Total vegetarians (vegans) must take vitamin B12 supplements, consume B12-fortified foods, or they will eventually become deficient.59,60 Contrary to some reports, seaweed and tempe do not provide B12. (Some forms of blue-green algae, such as spirulina, contain B12, but it is not in an absorbable state.61)

Vitamin B12 is available in three forms: cyanocobalamin, hydrocobalamin, and methylcobalamin. The first is the most widely available and least expensive, but some experts think that the other two forms are preferable.

Caramont. org 2

Severe B12 deficiency can cause anemia and, potentially, nerve damage. The latter may become permanent if the deficiency is not corrected in time. Anemia most often develops first, leading to treatment before permanent nerve damage develops. However, folate supplements can get in the way of this "early warning system." This is why people are cautioned against taking high doses of folate without medical supervision. When taken at a dosage higher than 400 mcg daily, folate can prevent anemia caused by B12 deficiency, thereby allowing permanent nerve damage to develop without any warning. More mild deficiencies of vitamin B12 may cause elevated levels of homocysteine in the blood, potentially increasing risk of heart disease. (See the homocysteine article for more information.) Mild B12 deficiency (too slight to cause anemia) may also impair brain function.24,25

Therapeutic Dosages

For correcting absorption problems caused by medications, taking vitamin B12 at the level of dietary requirements should suffice.

For other purposes, enormously higher daily doses-ranging from 100 to 2,000 mcg-are sometimes recommended.

Therapeutic Uses

It appears that individuals who take medications that dramatically lower stomach acid, such as H2 blockers or proton pump inhibitors, would benefit by taking B12 supplements.18-23 Other individuals likely to be deficient in B12, such as the elderly, or those taking the medications listed in Requirements/Sources, might well benefit from a daily B12 supplement to prevent B12 deficiency.

For pernicious anemia, B12 injections are traditionally used but research has shown that oral B12 works just as well, provided you take enough of it (between 300 and 1,000 mcg daily).26-29

Weak evidence suggests that B12 supplements may improve sperm activity and sperm count; on this basis, they could be useful for male infertility.30,31 Some cases of recurrent miscarriage might be due to vitamin B12 deficiency.62

Vitamin B12 is widely recommended as a treatment for asthma,32 but there is little real evidence that it is effective. On the basis of weak and sometimes contradictory evidence, vitamin B12 has been suggested for HIV,33-37amyotrophic lateral sclerosis,38diabetic neuropathy,39,40multiple sclerosis (MS),41-45restless legs syndrome,46,47 and tinnitus.48

Some evidence suggests that people with vitiligo (splotchy loss of skin pigmentation) might be deficient in vitamin B12 and supplementation along with folate may be helpful.52,53 However, the evidence is very weak and not all studies agree.54

Some alternative practitioners recommend the use of injected vitamin B12 for Bell's palsy. However, the only scientific support for this approach comes from one study that was not double-blind.63 (For information on the importance of a double-blind design, see Why Does the Natural Pharmacist Rely on Double-blind Studies?)

Vitamin B12 is also sometimes recommended for numerous other problems, including depression, osteoporosis, and periodontal disease, but there is essentially no evidence as yet that it really works.

A double-blind trial of vitamin B12 for seasonal affective disorder (SAD-a type of depression related to lack to lack of light during the winter) failed to find evidence of benefit.58

Another study failed to find evidence that vitamin B12 improved general sense of wellbeing among seniors with signs of mild B12 deficiency.64

Although vitamin B12 has been proposed as a treatment for Alzheimer's disease, this recommendation is based solely on the results of one small, poorly designed study.49 More recent and better-designed studies found little to no benefit.50,51

Comment 3

What Is the Scientific Evidence for Vitamin B12?

Male Infertility

Vitamin B12 deficiencies in men can lead to reduced sperm counts and lowered sperm mobility. For this reason, B12 supplements have been tried for improving fertility in men with abnormal sperm production. In one double-blind study of 375 infertile men, supplementation with vitamin B12 produced no benefits on average in the group as a whole.55 However, in a particular subgroup of men with sufficiently low sperm count and sperm motility, B12 appeared to be helpful. Such "dredging" of the data is suspect from a scientific point of view, however, and this study cannot be taken as proof of effectiveness.

Safety Issues

Vitamin B12 appears to be extremely safe. However, in some cases very high doses of vitamin B12 can cause or worsen acne symptoms.56,57

Interactions You Should Know About

If you are taking

Medications that reduce stomach acid such as H2 blockers-such as Zantac (ranitidine)-and proton pump inhibitors-such as Prilosec (omeprazole)-colchicine, AZT, or if you are exposed to nitrous oxide anesthesia: You may need extra B12.

Metformin or phenformin: You may need extra B12. Another option is to take extra calcium, which may in turn improve B12 absorption.

Slow-release Potassium Supplements:You may need extra B12. ←

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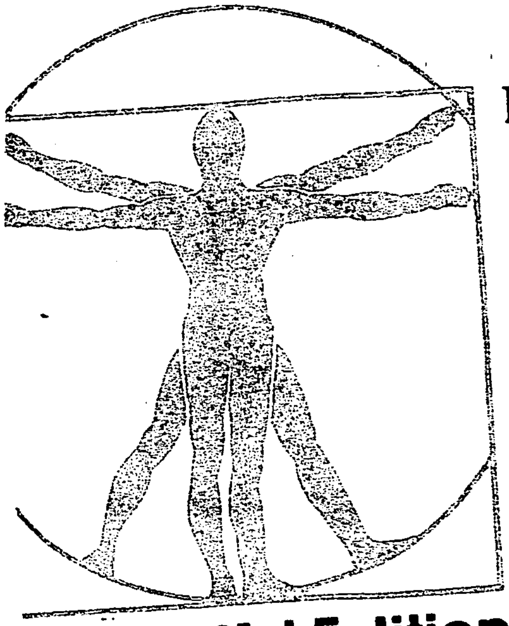

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The brush border membrane is impermeable to all but monosaccharides, and these are transported by specific carrier proteins. Glucose and galactose share the same carrier and are more readily transported than is fructose. Other monosaccharides such as mannose are not transported and remain in the lumen. If the concentrations of these unabsorbed monosaccharides become high enough to raise the intraluminal osmotic pressure, water is drawn from the interstitial fluid and diarrhea may result.

As with the proteins, the transport of glucose and galactose is linked to Na^+ (see Fig. 73–17). The carrier protein involved in the transport of fructose is completely separate and appears to be sodium independent. The rate-limiting step in the absorption of the monosaccharides is the availability of the carrier protein, since saturation of glucose uptake can be easily demonstrated.

Absorption of Lipids

The absorption of fat is nearly complete, with up to 95% of ingested fat being transported through the epithelium. Three mechanisms have been suggested to account for the passive diffusion of fatty acids and monoglyceride across the brush border. First, the entire micellar aggregate could be transported through the membrane into the cytoplasm by pinocytosis. This seems unlikely for several reasons, including the fact that different components of the micelle are absorbed at different levels of the intestine. This is particularly relevant when considering the bile salts, which are an integral component of the micelle; bile salts are absorbed in significant quantities only in the ileum, and not in the jejunum where most lipid absorption occurs. Second, it is possible that the micelle binds to a surface component on the brush border and that lipid molecules solubilized within the micelle diffuse through the membrane. The micelle remains bound to the brush border and spans the unstirred water layer, acting as a conduit, passing digested monoglyceride and fatty acids through to the membrane. The factors causing dissociation of the micelle or absorption of different lipids have yet to be explained. In the third model, the micelle does not bind to the brush border, and solubilized lipid is shuttled through an aqueous stage prior to traversing the membrane. Of the three possibilities, the last is favored according to the available experimental evidence.

Once within the cytoplasm, the fatty acids and monoglyceride are re-esterified in the endoplasmic reticulum to triglyceride. The newly synthesized triglyceride and apoprotein, cholesterol, phospholipids, and the fat-soluble vitamins form chylomicrons, which are the intracellular version of the micelles (Fig. 73–19). Chylomicrons are smaller than micelles and are released through the basolateral membrane to enter the lacteals that drain into the lymph system. The chylomicrons do not enter the blood stream directly, because the capillaries are surrounded by a basement membrane of polysaccharides that act as a barrier. From the lymph, the chylomicrons enter the thoracic duct and flow directly to the heart, bypassing the hepatic portal system.

Absorption of Fat-Soluble Vitamins

The fat-soluble vitamins A, D, E, and K are taken up into the luminal micelles and transferred to the brush border membrane. The vitamins diffuse across the membrane into the cytoplasm of the enterocyte, where they are incorporated into the chylomicrons and released into the lymph system.

Absorption of Bile Salts

The absorption of bile acids is divided between active transport in the distal ileum (60%) and passive diffusion through the epithelium of the entire length of the small intestine (40%). The active process removes the majority of the conjugated ionized bile salts that have been active in micellar formation, while the passive diffusion removes any uncomplexed bile acids. The active transport system is saturable and there is competition between the different forms for absorption.

Absorption of Water-Soluble Vitamins

The majority of the water-soluble vitamins are absorbed either by passive diffusion or by carrier-mediated (active) transport in the lower jejunum and upper ileum. The exception is vitamin B_{12} (cobalamin), a large, highly charged compound. The absorption of cobalamin requires the interaction between intrinsic factor and R protein secreted from the stomach (Fig. 73–20). Cobalamin binds to R protein initially in the stomach and thus is shielded from degradation by the proteases in the duodenum. The R protein is differentially digested in the duodenum, and cobalamin is released and

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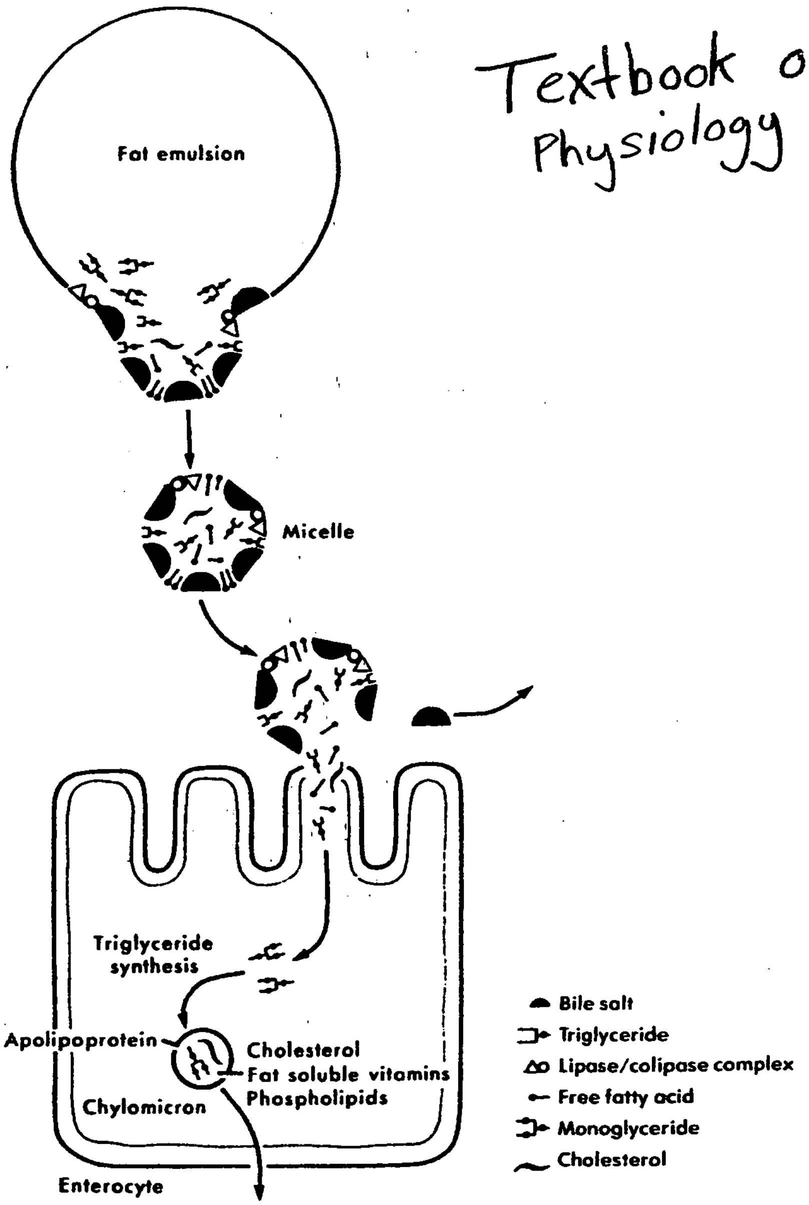

Figure 73–19 The absorption of fat in micelles.

bound to intrinsic factor. The intrinsic factor–cobalamin complex is transported distally to the terminal ileum, where intrinsic factor binds to specific brush border receptors. Cobalamin is then transferred through the membrane by a specific carrier protein linked to the receptor and liberated into the cytoplasm. Cobalamin diffuses into the circulation, where it complexes with transcobalamin, a specific carrier protein. Intrinsic factor then dissociates from the brush border and is eliminated in the feces. Intrinsic factor is essential in the absorption of cobalamin, and a decrease in its production will result in the onset of pernicious anemia. Pernicious anemia is caused by decreased levels of cobalamin, which is essential for normal erythrocyte maturation.

Absorption of Nucleotides

The hydrolysis of DNA and RNA yields polynucleotides, which are further hydrolyzed by

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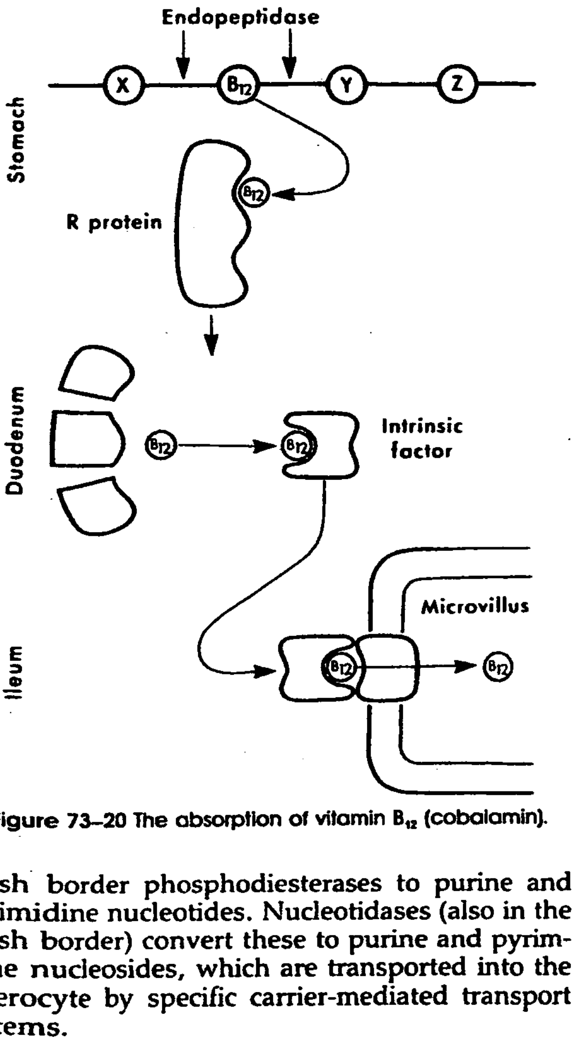

Figure 73–20 The absorption of vitamin B_{12} (cobalamin).

brush border phosphodiesterases to purine and pyrimidine nucleotides. Nucleotidases (also in the brush border) convert these to purine and pyrimidine nucleosides, which are transported into the enterocyte by specific carrier-mediated transport systems.

Water and Electrolyte Balance

The ability of water and electrolytes to pass through the intestinal epithelium varies, with the duodenum being the most permeable and the ileum relatively impermeable. The difference is the result of changes in the tight junctional complexes at the apical region of the enterocytes. In the duodenum the microfilament system underlying the microvilli is relatively sparse, leading to "leaky" tight junctions through which water and electrolytes can diffuse. Ions such as Na^+ and K^+ pass readily through the leaky tight junctions in either direction, whereas the movement of Cl^- and HCO_3^- and divalent ions such as Ca^{2+} is limited. The movement of ions through the tight junctional regions does not involve the brush border membrane, and the water and electrolytes absorbed or excreted move into and out of the interstitial fluid. This type of transport is termed *paracellular*, since it does not directly involve the epithelial cells, and net movement is controlled by the luminal osmotic pressure. The majority of water absorption occurs in the duodenum and jejunum by this paracellular route. The enterocytes lining the villi will secrete water and electrolytes if the interstitial fluid pressure exceeds that of the fluid in the intestine by more than 3 mm Hg. The composition of this fluid is similar to that of plasma.

In the crypt region, an active secretion of Cl^- and HCO_3^- occurs from the immature enterocytes. It appears that as the enterocytes mature, the transport characteristics reverse, because the mature cells absorb, rather than secrete, these ions. Secretion of the anions is stimulated by cholera toxin, acetylcholine, VIP, and 5-HT. The last three stimulants are released from components of the intrinsic innervation; 5-HT may also work in a paracrine fashion, being released from the epithelial enterochromaffin cells.

Chloride. In the upper intestine, Cl^- moves into and out of the lumen by the paracellular route, net movement being controlled by solute concentration. In the ileum, Cl^- is actively absorbed as NaCl and by an HCO_3^-/Cl^- exchange system.

Potassium. K^+ ions are absorbed through the jejunal epithelium by paracellular movement. The ions diffuse down a concentration gradient from 14 to 16 mEq/ℓ in the lumen to 3 to 6 mEq/ℓ in blood.

Bicarbonate. The upper small intestine absorbs bicarbonate in an indirect fashion. CO_2 diffuses from the lumen into the enterocyte where with H_2O it is converted to H_2CO_3 (carbonic acid) by carbonic anhydrase. This dissociates to H^+ and HCO_3^-, and the HCO_3^- diffuses into the bloodstream. In the ileum, HCO_3^- is actively secreted into the lumen in exchange for Cl^-.

Sodium. The small intestine is extremely efficient in absorbing Na^+ ions. Of the Na^+ entering the system, 60% is absorbed in the jejunum, 35% in the ileum, and the remainder in the colon. There are several absorption systems involved, all driven by the Na^+,K^+-ATPase pump in the basolateral membrane. The activity of this pump, which moves 3 Na^+ ions out of the cell for 2 K^+ ions inward, creates an electrochemical gradient favoring Na^+ absorption from the apical side. Na^+ ions can be transported into the cell solely by the electrochemical gradient, without involving transport of other molecules (uncoupled). A second

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